

Corticosteroids: A controversial therapy for coronavirus disease 2019

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) has become a pandemic within months. It is a self-limited viral illness in most cases, but it has spread across the world with rising numbers of deaths. Approximately 10% patients with COVID-19 required hospital admission, of whom about 10% were admitted to the intensive care unit (ICU) for acute respiratory distress syndrome (ARDS).^[1–4] While COVID-19 appeared to have higher mortality in older male patients with comorbidities, young patients with no comorbidities were also at risk of critical illness including ARDS, multi-organ failure and death. Thus, focus on treatment for severe COVID-19 patients would improve the cure rate and reduce mortality.^[5] However, little data is available that describe the pathophysiology of severe COVID-19, and no drug therapies of proven efficacy exist yet.

CYTOKINE STORM

Among the first reported 41 patients with COVID-19, 32% (13) patients were admitted to ICU and 15% (6) died. Compared with severe acute respiratory syndrome (SARS, with increased levels of interleukin [IL]-1 β , IL-6, IL-12, interferon [IFN]- γ , interferon-gamma-inducible protein [IP]-10, and monocyte chemoattractant protein [MCP]-1)^[7] and middle east respiratory syndrome (MERS, with increased levels of IFN- γ , tumor necrosis factor [TNF]- α , IL-15, and IL-17),^[8] the patients with COVID-19 had high levels of IL1 β , IFN γ , IP10, and MCP1, probably leading to activated T-helper 1 (Th1) cell responses. Furthermore, the

patients requiring ICU admission had higher concentrations of granulocyte colony stimulating factor (G-CSF), IP-10, MCP-1, macrophage inflammatory protein 1A (MIP-1A), and TNF- α than those who did not.

Cytokine storm was known as cytokine cascade. It was first proposed by Ferrara in 1993 in graft-versus-host disease, which was an excessive immune response of the body to external stimuli such as viruses or bacteria.^[9] There are specific positive feedback mechanisms between cytokines and neutrophils and macrophages. Many cytokines such as TNF- α , IL-1, IL-6, IL-8, IL-12, IFN- α , IFN- β , IFN- γ , and MCP-1 are released rapidly after infection, which is the main cause of ARDS and multiple organ dysfunction syndrome (MODS). COVID-19, SARS, MERS, and H1N1 influenza virus infections could lead to cytokine storm.

On the one hand, cytokine storm plays an important role in ARDS induced by viruses; the levels of IL-6, IL-17, IP-10, MCP-1, and IFN- α increased among patients with severe infection.^[10,11] On the other hand, viruses could also interfere with cytokine signaling and contribute to cytokine storm.^[12,13] The cytokines such as IL-1 β , IL-6, and TNF- α are responsible for amplifying the inflammatory response, while the cytokines IL-4, IL-10, IL-13, etc. suppress inflammatory responses. Virus clearance depends on inflammatory response, but excessive inflammation caused by uncontrolled cytokine storm induces multiple organ injury.^[14]

In a retrospective single-center study, the absolute value of lymphocytes decreased

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in most of the 99 patients recruited in Wuhan, China, indicating that like SARS, COVID-19 mainly impaired lymphocytes, especially T lymphocytes. The virus spreads through the respiratory mucosa and infects multiple cell types, induces cytokine storm, generates a series of inappropriate immune responses, and causes alterations in peripheral immune cells such as lymphocytes. Some patients who progressed to ARDS presented cytokine storm and diffuse alveolar damage.^[15] Eleven percent patients in the report eventually developed MODS, characterized by elevated creatinine, coagulation disorder, changes in liver enzyme expression, circulatory shock, vascular leakage, and disseminated intravascular coagulation.^[16] Therefore, early identification of the cytokine storm and timely treatment of critical cases are of crucial importance.

CORTICOSTEROIDS

Very limited direct evidence on corticosteroid therapy in patients with COVID-19 has been reported. Indirect evidence from related conditions showed benefits and harms. Corticosteroids are the most commonly used drug therapy to suppress cytokine storm caused by various diseases. Based on limited data, there was no clear benefit and potential harm from corticosteroids; corticosteroid therapy is still controversial.

The World Health Organization guideline for the clinical management of severe acute respiratory infections with suspected COVID-19 recommended that routine corticosteroids should be avoided unless they are indicated for another reason.^[17] Carefully designed randomized controlled trials (RCTs) and prospective outcome registries are needed to determine the dose, route, timing, and duration of such treatment on the prevention of clinical deterioration and to better understand the potential harms associated with its use.

Pros

In a retrospective cohort study including 201 patients with COVID-19-related ARDS in China, treatment with corticosteroids (methylprednisolone) decreased the risk of death (hazard ratio [HR] 0.38, 95% CI 0.20–0.72).^[18] Critically ill patients were more likely to be given corticosteroids in the study. However, administration of corticosteroids was associated with reduced risk of death in patients with ARDS. These findings suggested that corticosteroid treatment may be beneficial for patients with COVID-19 who have developed ARDS. However, the study indicated that the results should be dealt with caution because of the potential bias and residual confounding in this observational study with a small sample size.

Recently, a systematic review and meta-analysis of corticosteroid treatment among ARDS patients included one small cohort study of COVID-19 and seven RCTs of non-COVID-19 patients (risk ratio [RR] 0.72, 95% CI 0.55–0.93, mean difference 17.3% lesser, low-quality evidence).^[19] Corticosteroids were associated with reduced mortality of patients with COVID-19-related ARDS by more than 15% and reduced the duration of mechanical ventilation. In addition, RCTs in community-acquired pneumonia suggested that corticosteroids may reduce mortality (RR 0.70, 95% CI 0.50–0.98, 3.1% lesser; very low quality evidence) and length of hospital stay (mean difference [MD] 3.6 days shorter, 95% confidence interval [CI] 0.02–7.2 days shorter),^[20–22] but increase adverse effects of hyperglycemia (risk increase 8.1%, 95% CI 0.7%–16.2%).^[11,23,24] But for COVID-19 patients without ARDS, evidence of very low quality from two observational studies showed increase in mortality associated with corticosteroids (HR 2.30, 95% CI 1.00–5.29, mean difference 11.9% greater), which was in line with several observational studies of influenza. Another retrospective cohort study reported that short-term and low-dose treatment of corticosteroids among non-severe COVID-19 patients during the stage of clinical deterioration may possibly prevent disease progression, while having a negligible impact on the viral clearance.^[25]

The indirect evidence from SARS and MERS should be considered. A systematic review^[26] reported 15 studies, 13 of which were inconclusive on the benefits of corticosteroids at the early stage of the disease. One RCT reported delayed viral clearance associated with corticosteroid use in SARS. A study of corticosteroid treatment during the SARS outbreak indicated that no benefit was found for corticosteroids prescribed early in the disease process and might lead to delayed viral clearance.

Recently, an inspiring RCT showed that dexamethasone at a dose of 6 mg once daily for up to 10 days resulted in one-third lower 28-day mortality than usual care in COVID-19 patients who were receiving invasive mechanical ventilation or oxygen; but no benefit and possible harm were found in mild patients who were not receiving respiratory support. This study may have profound effects on the recommendations of corticosteroids in COVID-19 patients.^[27]

Cons

A systematic review of observational studies of corticosteroids administered to patients with SARS reported no survival benefit and possible harms (avascular necrosis, psychosis, diabetes, and delayed viral clearance).^[28] A study of patients receiving corticosteroids for MERS found no effect of corticosteroids on mortality but delayed

lower respiratory tract clearance of MERS-CoV.^[29] A systematic review of observational studies of influenza found a higher risk of mortality and secondary infections with corticosteroids; the evidence was judged as very low to low quality due to confounding by indication.^[30] A subsequent study that addressed this limitation by adjusting for time-varying confounders found no effect of corticosteroids on mortality.^[31]

Generalizing evidence from ARDS studies to viral lung injury is problematic because these trials typically include a majority of patients with ARDS of non-pulmonary or sterile cause.^[32] A review of treatments for ARDS of any cause, based on six studies with a total of 574 patients, concluded that insufficient evidence existed to recommend corticosteroid treatment.^[33] Russell *et al.* commented that the benefits derived from corticosteroids in the treatment of respiratory infection due to respiratory syncytial virus (RSV), influenza, SARS, or MERS were limited. The available observational data suggested increased mortality and secondary infection rates in influenza infection, impaired viral clearance in SARS and MERS, and increased rates of complications due to corticosteroid therapy in survivors. They concluded that corticosteroid treatment should not be used for the treatment of COVID-19 induced lung injury or shock outside of a clinical trial.^[34]

Recommendation

In practice, clinicians tend to use corticosteroids in critical disease. The selective bias in the observational study may result in an increase in mortality among the corticosteroid-treated group. Up until now, clinical evidence was not convincing to recommend against corticosteroids for COVID-19.

According to “The diagnosis and treatment of COVID-19 (version 7)” and “Expert consensus on the use of corticosteroid in patients with 2019-nCoV pneumonia” by National Health Commission and Chinese Thoracic Society,^[35,36] if the patient’s dyspnea and chest imaging progresses, oxygen saturation significantly decreases, CRP increases, and conventional treatment could not prevent the progress of the disease, which indicate cytokine storm, low-dose and short-term (3–5 days) use of corticosteroids (methylprednisolone 1–2 mg/kg per day) is recommended. However, the timing of corticosteroid use is essential. The alterations of lymphocyte, CRP, oxygenation index, and imaging manifestations should be considered carefully. After improvement, the dose should be reduced slowly until it is stopped.

Corticosteroids should be administered with caution among patients who have the following conditions: (1) diabetes and receiving oral medication or insulin treatment;

(2) allergy for methylprednisolone, hydrocortisone, dexamethasone, or other corticosteroids; (3) refractory hyperglycemia; (4) epilepsy or delirium; (5) glaucoma; (6) active gastrointestinal bleeding in the past 3 months; (7) hypokalemia; (8) secondary bacterial or fungal infection; (9) immunosuppressive status (*e.g.*, HIV infection within 1 month after chemotherapy, radiotherapy, or surgery); and (10) severe lymphopenia (peripheral blood lymphocytes <300/ μ L).^[37]

It should be noted that when more corticosteroids are used, the adverse events are worse. A previous study of 1137 SARS cases from 10 trials showed that higher cumulative dose and longer duration of steroid treatment in SARS patients were more likely to cause osteonecrosis.^[37]

CONCLUSION

Many severe COVID-19 patients die from complications such as ARDS and MODS caused by cytokine storm. There is no specific treatment for cytokine storm in clinical practice so far. Corticosteroids are the most commonly used therapy to suppress cytokine storm in various diseases. Based on limited data, corticosteroid therapy for severe COVID-19 is still controversial. Short-course and low-dose applications of corticosteroids in severe COVID-19 patients during the stage of clinical deterioration were recommended. Corticosteroids combined with antiviral therapy, targeted immunotherapy, and traditional Chinese medicines may reduce mortality of severe COVID-19 patients. In addition, active prevention and treatment of complications and respiratory and circulation support are very important measures in the treatment of severe patients with COVID-19.

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Conflict of Interest

All authors declare that they have no conflict of interest.

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